UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,752	01/11/2001	Johannes Jacobus Voorberg	294-86	5298

7590 07/03/2006

Ronald J Baron
Hoffmann & Baron
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,752	VOORBERG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87-88 and 91-100* is/are rejected.

7)☒ Claim(s) *89 and 90* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Attachment I*.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/9/06 has been entered.

2. Claims 87-100 are pending and under examination as they read on a polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, which polypeptide comprises the variable region of the heavy chain of a human antibody with factor VIII specificity or parts thereof which at least includes the CDR3 region and a pharmaceutical composition thereof.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 94-95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The recitation " binds the heavy chain of factor VIII" in claim 94 and the recitation " binds the heavy chain of factor VIII consisting of the A1 domain, the A2 domain and the B domain of factor VIII" in claim 95, are ambiguous, claims 94 and 95 depends from claim 87, which recites VH sequences that only bind to the light chain of factor VIII. It is unclear how those sequences would bind to the heavy chain of factor VIII.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 87-88, and 91-99 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

A. The phrase "An isolated polypeptide capable of specific binding to factor VIII and comprising a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody; wherein the heavy

chain variable region comprises a sequence selected from the group consisting of SEQ IDNO: 24, SEQ ID NO: 26, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37 and SEQ ID NO: 52" claimed in claim 87,

B. The phrase "which is capable of interfering with the activity of factor VIII inhibitors, and wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 24 and SEQ ID NO: 26" claimed in claim 88.

Represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 3/9/06 does not point to the specification for support for the newly added limitations "An isolated polypeptide capable of specific binding to factor VIII and comprising a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody; wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ IDNO: 24, SEQ ID NO: 26, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37 and SEQ ID NO: 52" as claimed in claim 87. However, the specification does not provide a clear support for such limitation. It is not contemplated in the specification that the germ lines DP10 (SEQ ID NO: 24), DP-14 (SEQ ID NO: 26), DP-15 (SEQ ID NO: 31), DP31 (SEQ ID NO: 33), DP49 (SEQ ID NO: 35), DP37 (SEQ ID NO: 37) and DP47 (SEQ ID NO: 52) polypeptides capable of specific binding to factor VIII and comprising a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody. Further, it is not contemplated in the specification that SEQ ID NO: 24 (DP-10) or SEQ ID NO: 26 (DP-14) germ lines are capable of interfering with the activity of factor VIII inhibitors. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

7. Claims 87-88 and 91-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide capable of specific binding to factor VII and interference with the activity of factor VIII inhibitors, wherein the polypeptide comprises a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody, wherein the heavy chain variable region omprises a sequence selected from the group consisting of SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 32, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 51and SEQ ID NO: 53 and a composition thereof, does not reasonably provide **enablement** for an isolated polypeptide capable of specific binding to factor VIII and comprising a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody, wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 24, 26, 31, 33, 35, 37, and 52 in claim 87, which is capable of interfering with the activity of factor VIII inhibitors, and wherein the heavy chain variable region comprises sequence selected from the group consiting of SEQ ID NO: 24 and SEQ ID NO: 26 in claim 88. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification on page 25, lines 30-34 discloses that the CDR3 region of the clones can determine the specificity of these antibodies for the factor VIII light chain. Further, the specification under Example 2, discloses that the VH region of the claimed antibody is important in determining the binding activity of the scFv to factor VIII. Since the source of light chain variable regions can be any light chain variable region of a human antibody. However, claims 87 and 88 recite that the VH of the claimed polypeptide is the germ line segments of DP10 (SEQ ID NO: 24), DP-14 (SEQ ID NO: 26), DP-15 (SEQ ID NO: 31), DP31 (SEQ ID NO: 33), DP49 (SEQ ID NO: 35), DP37 (SEQ ID NO: 37) or DP47 (SEQ ID NO: 52). These germ line segments lack the crucial CDR3 (see figures 4, 9 and 11). Yet, Applicant claims that these germ line segments have the ability to bind to factor VIII. Since the germ lines lack the crucial CDR3 feature that determines the specificity of the claimed antibodies and since VL region lack of importance, the skill in the art would not expect the claimed germ line segments to specifically bind factor VIII. Further, the specification fails to provide sufficient guidance as how such germ line segments would bind to factor VIII.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979) (of record). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Regarding the pharmaceutical compositions of claims 98-100, it has been established that in the absence of a correlation between the in vitro and in vivo efficacy the person having ordinary skill in the art has not basis for perceiving these efficacy. "First, although appellants' specification describes certain in vitro experiments, there is no correlation on this record between in vitro experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals" (emphasis added). Ex parte Maas, 9 USPQ2d 1746.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 87-88 and 92-99 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/08336.

The `336 publication teaches an immunoglobulin comprises OF71.2 (claimed and published SEQ ID NO: 24) having the amino acid depicted in figure 5(B) (claimed SEQ ID NO: 24) (see published claims 1-6 and 15-17, pg. 68, published SEQ ID NO: 24 and attached sequence alignment in particular). The ` 336 publication teaches a pharmaceutical composition comprising the antibody and a carrier (see published claim 17 in particular). It is noted that the referenced antibody comprises both the heavy and light chains. The `336 publication teaches that the referenced sequences are IgG (see page 51, line 5-7 in particular).

While the prior art teachings may be silent as to the "capable of specific binding to factor VIII" claimed in claim 87, " capable of interfering with the activity of factor VIII inhibitors" claimed in claim 88, "specifically binds the heavy chain of factor VIII" in claim 94, " specifically binds a domain of the heavy chain of factor VIII consisting of the A1 domain, the A2 domain and the B domain of factor VIII" in claim 95, "specifically binds the light chain of factor VIII" in claim 96, "specifically binds a region of the light chain of factor VIII consisting of the A3 domain, the C1 domain and the C2 domain of factor VIII" per se; the product in the reference is the same as the claimed product. Therefore, these limitations are considered inherent properties.

When a claim recites using an old composition or structure (e.g. antibodies comprising SEQ ID NO: 24) and the use is directed to a result or property of that composition or structure (binds factor VIII), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

The reference teachings anticipate the claimed invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 87 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/08336 in view of Bird *et al* (1988) (off record).

The teachings of WO `336 publication, have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a single chain Fv fragment in claim 91.

Bird *et al* teach a single chain antigen binding proteins composed of an antibody variable light – chain amino acid sequence (V_L) tethered to a variable heavy –chain sequence (V_H) by a designed peptide that links the carboxyle terminus of the V_L sequence to the amino terminus of the V_H sequence. Bird *et al* further teach that the single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion (see the entire document and page 426, left column, 2nd paragraph in particlular)).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by `336 publication as a single chain antibody as taught by the Bird *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion as taught by Bird *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore,

the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Claims 89-90 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 20, 2006

Maher Haddad

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600